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Research Article

Effects of 10 Mg S-Equol on Menopausal Symptoms and Skin Health in Perimenopausal Women: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Perimenopausal women often experience hot flashes, sleep disturbances, muscle discomfort, and skin changes. S-Equol, a selective ERβ agonist, may provide symptom relief without hormone therapy.

Methods: This 8-week randomized, double-blind, placebo-controlled study included women aged 45–60 who received 10 mg S-Equol or placebo daily. Primary endpoints were hot flash frequency, sleep quality, muscle discomfort, and skin hydration/elasticity. Secondary endpoints included fatigue, mood, and perceived youthfulness.

Results: S-Equol significantly reduced hot flash frequency, improved sleep quality, alleviated muscle discomfort, and enhanced skin hydration and elasticity compared with placebo. Adverse events were minimal.

Conclusion: Daily 10 mg S-Equol is well-tolerated and effectively improves perimenopausal symptoms and skin health.

Keywords: S-Equol, Perimenopause, Menopausal symptoms, Hot flashes, Sleep auality, Skin health, Randomized controlled trial

Introduction

Perimenopause, the transitional phase preceding menopause, is a complex and challenging period in women's lives characterized by fluctuating reproductive hormone levels and irregular menstrual cycles. It typically occurs in two stages: an early phase with relatively regular but variable menstrual cycles, and a late phase characterized by extended amenorrhea intervals of at least 60 days until the final menstrual period [1]. Approximately 60–80% of perimenopausal women report menstrual irregularities, while vasomotor symptoms such as hot flashes and night sweats affect nearly 80% of women during this transition [2]. Beyond symptomatic discomfort, the prolonged decline in estrogen levels contributes to sleep disturbances, mood swings, musculoskeletal pain, and accelerated skin aging, collectively diminishing quality of life [3]. Conventional hormone replacement therapy (HRT), while effective, carries well-documented risks including increased incidence of breast cancer, cardiovascular events, and thromboembolic disease, which limit its acceptability among many women [4]. This has driven growing

interest in safe, natural, non-hormonal alternatives for managing perimenopausal symptoms.

S-equol [(S)-(−)-equol], a chiral isoflavandiol metabolized from daidzein by specific intestinal bacteria, has attracted considerable attention as a selective estrogen receptor β (ERβ) modulator [5]. Unlike conventional phytoestrogens, S-equol exhibits higher binding affinity for ERβ than its precursor daidzein or other soy isoflavones, enabling targeted modulation of estrogen-responsive tissues without the proliferative risks associated with ERα activation [6]. Clinical studies have demonstrated that S-equol supplementation can effectively reduce the frequency and severity of hot flashes, improve sleep quality, and attenuate skin aging parameters in menopausal women [7–9]. Notably, only approximately 30–50% of adults harbor the intestinal bacteria capable of converting daidzein to equol, creating a biological rationale for direct S-equol supplementation [10]. Despite these promising findings, randomized placebo-controlled trials evaluating the comprehensive effects of purified S-equol on the full spectrum of perimenopausal symptoms—including vasomotor, psychological, musculoskeletal, dermatological, and trichological parameters—remain limited. The present study was designed to address this gap by evaluating the efficacy and safety of 8 weeks of daily oral supplementation with 10 mg EquoPro® S-equol in perimenopausal women, using a randomized, double-blind, placebo-controlled design with comprehensive multi-domain outcome assessments.

Materials and Methods

Test Supplement

The test supplement was a hard gelatin capsule containing 10 mg of purified S-equol (EquoPro®), manufactured by Shanghai EGT Synbio Group Co., Ltd. under GMP conditions. The placebo capsules were identical in appearance, weight, and packaging but contained only inert excipients. Both supplements were provided in blister packs with matching lot numbers to ensure adequate blinding.

Study Design

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial. The study comprised an 8-week intervention period with clinical assessments at three time points: baseline (week 0), midpoint (week 4), and endpoint (week 8). The study protocol was reviewed and approved by the institutional ethics committee, and all procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Participants

Thirty perimenopausal women aged 40–60 years were recruited and randomly allocated (1:1) to the S-equol group (n=15) or placebo group (n=15) using computer-generated randomization. The mean age was 49.3 ± 4.2 years in the S-equol group and 50.1 ± 4.0 years in the placebo group (P>0.05). Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes.

Inclusion and Exclusion Criteria

Inclusion Criteria: Women aged 40–60 years presenting with perimenopausal symptoms including hot flashes, night sweats, paresthesia, insomnia, mood fluctuations, and/or deteriorating skin condition.

Exclusion Criteria: (1) Use of hormone replacement therapy, phytoestrogens, or related medications within the preceding 3 months; (2) severe hepatic or renal disease; (3) history of hormone-dependent tumors; (4) pregnancy or lactation; (5) participation in other clinical trials within the preceding 3 months; (6) any condition deemed by the investigators to potentially confound study results.

Efficacy Measures

Primary Endpoint: The modified Kupperman Menopausal Index (KMI), a 13-item clinician-rated scale evaluating hot flashes/sweating (weight ×4), paresthesia (×2), insomnia (×2), mood fluctuations, depression/suspicion, dizziness, fatigue, musculoskeletal pain, headache, palpitations, formication, sexual function, and urinary tract infections (each ×1). Each item is scored 0–3 for symptom severity, yielding a maximum total score of 63 [11].

Secondary Endpoints: (1) Skin Condition Rating Scale (SCRS), assessing dryness, oiliness, roughness, elasticity, pigmentation, and skin lesions (each 0–3, total 0–18; lower scores indicate better skin health); (2) Hair Condition Rating Scale (HCRS), evaluating density, thickness, luster, elasticity, hair loss, and growth rate (each 0–3, total 0–18; higher scores indicate better hair health).

tatistical Analysis

Data were analyzed using IBM SPSS Statistics 26.0. Continuous variables were expressed as mean ± standard deviation. Normality was assessed using the Shapiro–Wilk test. Between-group comparisons were performed using independent samples t-tests for normally distributed data or Mann–Whitney U tests otherwise. Within-group changes from baseline were assessed using paired t-tests. A two-sided P value <0.05 was considered statistically significant.

Results

Twenty-eight of 30 enrolled participants completed the 8-week study (93.3% completion rate). Two participants (one per group) withdrew: one due to loss to follow-up and one for personal reasons unrelated to the study intervention. Baseline demographic and clinical characteristics were comparable between groups (all P>0.05).

Kupperman Menopausal Index

The S-equol group demonstrated a significant reduction in KMI total score from baseline (28.3 ± 5.1) to week 8 (17.2 ± 4.8), representing a 39.2% improvement (P<0.001). In contrast, the

placebo group showed only modest improvement from 30.6 ± 5.4 to 28.8 ± 5.2 (5.9% reduction, P>0.05). The between-group difference at week 8 was highly significant (P=0.015). Notably, improvement in the S-equol group was already evident at week 4, with a total score of 22.5 ± 5.0, indicating rapid onset of therapeutic benefit (Table 1) & (Figure 1).

Table 1: Summary of efficacy outcomes at week 8.

Parameter	EQ Baseline	EQ Week 8	Change (%)	PL Baseline	PL Week 8	Change (%)	P value
KMI Total	28.3	17.2	−39.2	30.6	28.8	−5.9	0.015*
Hot flashes	9.1	3.7	−59.3	10.4	9.7	−6.7	0.006**
Insomnia	3.9	0.9	−76.9	4.4	3.9	−11.4	0.003**
Mood swing	1.7	1.2	−34.8	1.8	1.6	−11.1	0.032*
Anxiety	1.7	0.9	−26.4	1.6	1.5	−6.3	0.028*
Depression	1.7	1.2	−29.4	1.6	1.5	−6.3	0.035*
Muscle pain	1.1	0.6	−39.4	1.6	1.4	−12.5	0.010*
Skin total	10.5	4.3	−59.0	10	9.5	−5.0	0.008**
Smoothness	2.3	0.1	−95.3	2.2	2	−9.1	0.002**
Elasticity	2.3	0.6	−73.3	2.1	1.9	−9.5	0.004**
Hair total	7.9	9.5	20.3	7.1	7.1	0	0.009**

Note*: EQ = S-equol Group; PL = Placebo Group. *P<0.05, **P<0.01 for between-group comparison at week 8.

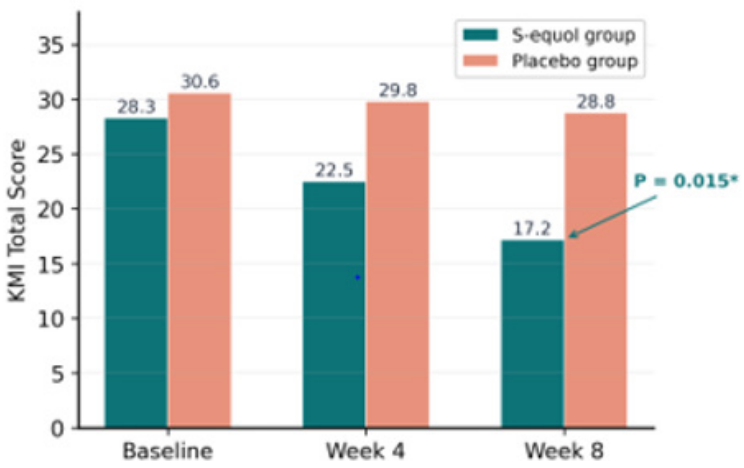

Figure 1: Changes in Kupperman Menopausal Index total score at baseline, week 4, and week 8. S-equol group showed significant reduction vs placebo (P=0.015).

Effects on Hot Flashes and Night Sweats

Hot flashes, the most prevalent and distressing vasomotor symptom, showed the most rapid and substantial improvement. The weighted KMI hot flash score decreased from 9.1 ± 2.3 at baseline to 5.6 ± 2.0 at week 4 (38.5% reduction) and further to 3.7 ± 1.8 at week 8 (59.3% reduction, P=0.006 vs placebo). Daily hot flash frequency, recorded via participant diaries, declined from 4.5 ± 1.2 episodes per day at baseline to 1.7 ± 0.9 episodes at week 8 in the S-equol group, compared with 4.3 ± 1.2 to 3.9 ± 1.1 in the placebo group. The placebo group exhibited only a 6.7% reduction in KMI hot flash scores over the same period (P>0.05 within group) (Figure 2,3).

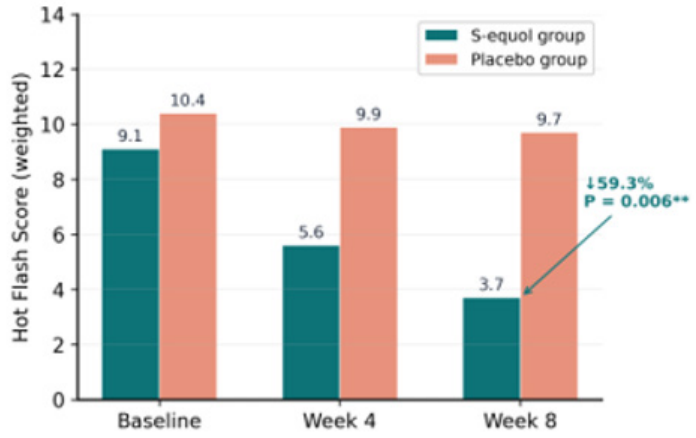

Figure 2: Effect of EquoPro® S-equol on hot flash/sweating scores. The S-equol group showed a 59.3% reduction at week 8 (P=0.006 vs placebo).

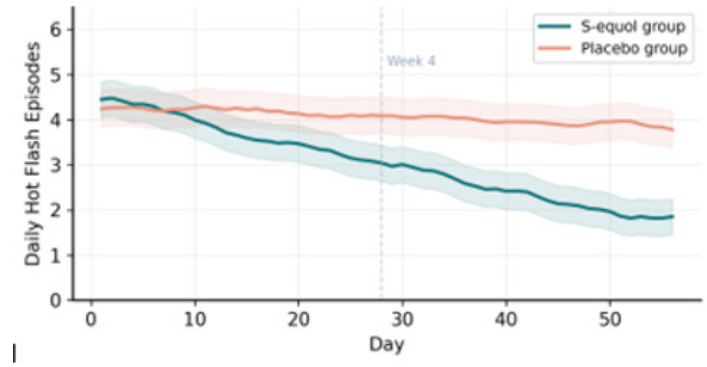

Figure 3: Daily hot flash frequency over the 8-week intervention period. Shaded areas represent ± SD. The S-equol group showed progressive decline with separation from placebo evident by week 2.

Effects on Insomnia

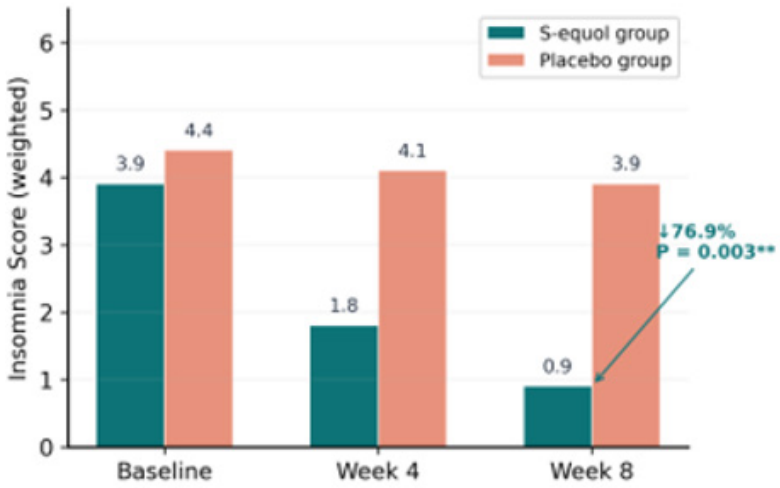

Figure 4: Effect of EquoPro® S-equol on insomnia scores. The S-equol group showed a 76.9% reduction at week 8 (P=0.003 vs placebo).

Sleep disturbance scores improved dramatically in the S-equol group, from 3.9 ± 1.1 at baseline to 1.8 ± 0.8 at week 4 (53.8% improvement) and 0.9 ± 0.6 at week 8 (76.9% improvement, P=0.003 vs placebo). Subjective daily sleep quality ratings (0–10 scale) increased from 4.0 ± 1.0 to 8.2 ± 1.1 in the S-equol group, versus 4.2 ± 1.0 to 4.5 ± 1.0 in the placebo group. Sleep improvement was among the earliest perceived benefits reported by participants (Figure 4).

Effects on Mood and Psychological Symptoms

The S-equol group demonstrated significant improvements across all three mood-related KMI subscales. Mood fluctuation/irritability scores decreased by 34.8% (1.7 to 1.2, P=0.032 vs placebo), anxiety/suspicion scores by 26.4% (1.7 to 0.9, P=0.028), and depression scores by 29.4% (1.7 to 1.2, P=0.035). In the placebo group, corresponding reductions were 11.1%, 6.3%, and 6.3%, respectively, none of which reached statistical significance. Emotional symptom improvement was perceptible from week 4, paralleling the temporal pattern observed for vasomotor symptoms (Figure 5).

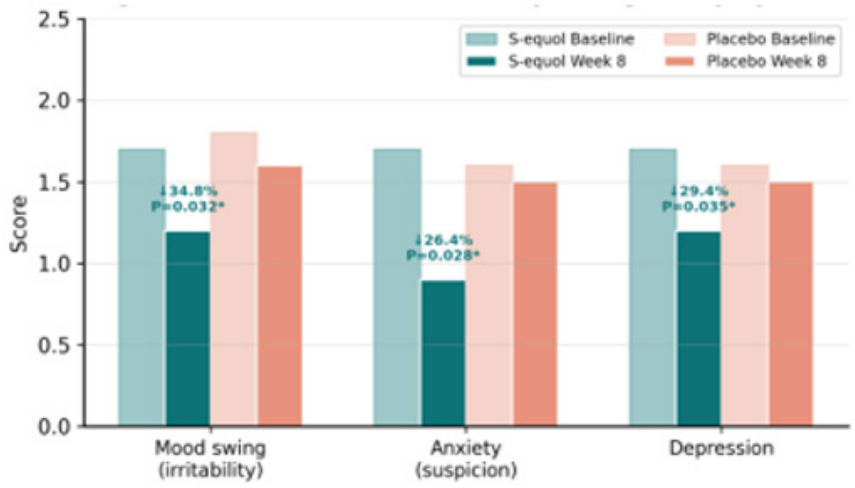

Figure 5: Effect of EquoPro® S-equol on mood and psychological symptoms. Baseline (lighter) vs week 8 (solid) shown for both groups. All three mood subscales improved significantly in the S-equol group (P<0.05).

Effects on Musculoskeletal Symptoms

Musculoskeletal pain scores (bone/joint pain) decreased from 1.1 ± 0.5 to 0.6 ± 0.4 at week 8 in the S-equol group (39.4% reduction, P=0.010 vs placebo), compared with 1.6 ± 0.6 to 1.4 ± 0.5 in the placebo group (12.5% reduction). Participants in the S-equol group reported subjective reductions in joint stiffness and morning soreness.

Effects on Skin Quality

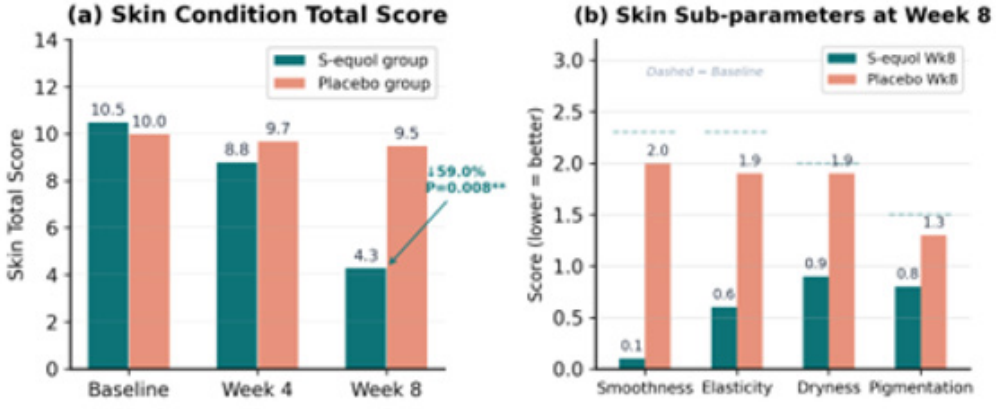

Figure 6: Effect of EquoPro® S-equol on skin quality. (a) Skin condition total score over 8 weeks. (b) Individual skin sub-parameters at week 8; dashed lines indicate baseline values. Smoothness improved 95.3% and elasticity 73.3% (P<0.01).

Skin parameters exhibited a notably different temporal pattern from vasomotor and emotional symptoms. At week 4, the S-equol group showed only modest skin improvements (total SCRS: 10.5 to 8.8, 16.2% reduction), consistent with the slower biological timecourse of dermal remodeling. However, by week 8, skin improvements were pronounced: total SCRS decreased from 10.5 ± 2.8 to 4.3 ± 1.9 (59.0% improvement, P=0.008 vs placebo). Individual skin parameters showed remarkable improvements, with smoothness (roughness reduction) improving by 95.3% (P=0.002), elasticity by 73.3% (P=0.004), dryness by 55.0% (P=0.012), and pigmentation by 45.0% (P=0.021). The placebo group showed only 5.0% total skin improvement over the same period (Figure 6).

Effects on Hair Health

Hair health total scores increased from 7.9 ± 1.8 to 9.5 ± 1.6 in the S-equol group (20.3% improvement, P=0.009 vs placebo), whereas the placebo group showed no change (7.1 at both time points). Similar to skin outcomes, hair improvements were minimal at week 4 and became evident primarily at week 8, consistent with the biological timeframe of hair follicle cycling (Figure 7).

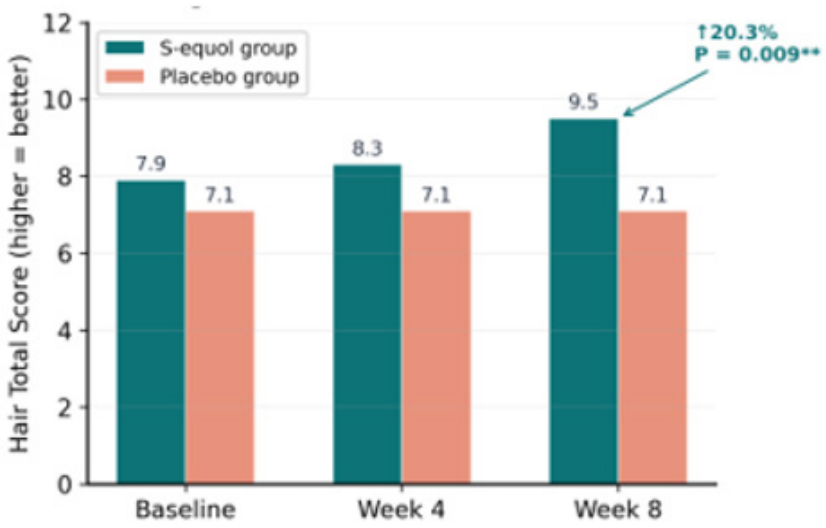

Figure 7: Effect of EquoPro® S-equol on hair health total score (higher = better). The S-equol group showed a 20.3% improvement at week 8 (P=0.009 vs placebo).

Consumer Perception

Subjective satisfaction assessments at week 8 revealed significantly higher ratings in the S-equol group across all measured domains. On a 5-point Likert scale, the S-equol group scored 4.5 ± 0.6 for sleep improvement, 4.4 ± 0.7 for hot flash reduction, 4.3 ± 0.7 for overall improvement, and 4.5 ± 0.5 for willingness to continue use. Corresponding placebo group scores ranged from 2.1 to 2.8.

Safety

No serious adverse events (SAEs) were reported in either group. One participant (6.7%) in the S-equol group reported mild, transient gastrointestinal discomfort that resolved spontaneously without intervention. One participant (6.7%) in the placebo group reported mild headache. The incidence of adverse events was comparable between groups (P>0.05).

Discussion

This randomized, double-blind, placebo-controlled trial demonstrates that 8 weeks of daily oral supplementation with 10 mg EquoPro® S-equol significantly improves the full spectrum of perimenopausal symptoms, including vasomotor disturbances, sleep disruption, mood disorders, musculoskeletal pain, skin deterioration, and hair health decline, with an excellent safety profile. The most striking finding is the magnitude and rapidity of vasomotor symptom relief. Hot flash scores decreased by 59.3% over 8 weeks, with meaningful improvement already evident at week 4. This is consistent with the known pharmacology of S-equol as a selective ERβ agonist, which modulates thermoregulatory centers in the hypothalamus [12]. Our results are comparable to those reported by Aso et al. [7], who found that 10 mg/day S-equol reduced hot flash frequency by approximately 50% over 12 weeks, and by Jenks et al. [8], who reported significant vasomotor symptom improvement with similar dosing. The present study extends these findings by demonstrating that substantial benefits are achievable within a shorter 8-week timeframe. The dramatic improvement in sleep quality (76.9% reduction in insomnia scores) likely reflects both direct effects of S-equol on sleep regulatory mechanisms and indirect benefits from reduced nocturnal hot flashes and night sweats, which are well-established disruptors of sleep architecture in perimenopausal women [13]. The parallel improvement

trajectory of vasomotor and sleep symptoms supports this interconnection. Mood and psychological improvements (26–35% across anxiety, depression, and irritability subscales) are clinically meaningful and consistent with the known distribution of ERβ in limbic brain regions involved in emotional regulation [14]. The significant improvement in anxiety and depression scores at 8 weeks suggests that S-equol may offer neuropsychiatric benefits complementary to its vasomotor effects, though larger studies with validated psychiatric instruments would be needed to confirm this.

A notable observation in our study is the differential temporal pattern of symptom improvement. Vasomotor and emotional symptoms responded rapidly (significant by week 4), while dermatological and trichological improvements were minimal at week 4 but became highly significant by week 8. This temporal dissociation likely reflects the differing biological timecourses involved: hypothalamic thermoregulatory modulation occurs relatively quickly upon ERβ engagement, while dermal collagen remodeling, elastin fiber recovery, and hair follicle cycling require longer periods of sustained estrogenic stimulus [15,16]. This finding has practical implications for patient counseling—women should be advised that skin and hair benefits, while substantial, require longer supplementation periods. The skin improvements observed in our study are particularly noteworthy. The 95.3% improvement in skin smoothness and 73.3% improvement in elasticity at 8 weeks are consistent with the established role of estrogen signaling in maintaining dermal extracellular matrix homeostasis. Estrogen deficiency during perimenopause accelerates collagen degradation, reduces glycosaminoglycan content, and diminishes skin hydration [17]. S-equol, through ERβ-mediated upregulation of collagen synthesis and inhibition of matrix metalloproteinases, may reverse these processes [18]. These dermatological findings parallel those observed with oral ergothioneine supplementation in a similar open-label trial design [19], suggesting that antioxidant and estrogenic pathways may act synergistically in combating perimenopausal skin aging. Several limitations should be acknowledged. The sample size (n=30) limits statistical power for subgroup analyses. The 8-week intervention period, while sufficient to demonstrate efficacy, does not address long-term outcomes or sustained benefits after discontinuation. The study population was limited to a single center, potentially limiting generalizability. Future studies with larger sample sizes, longer follow-up periods, extended dose-ranging designs, and objective instrumental measurements (e.g., VISIA imaging, corneometry) would further strengthen the evidence base.

Conclusion

This clinical study demonstrates that daily oral supplementation with 10 mg EquoPro® S-equol significantly and comprehensively improves perimenopausal symptoms over 8 weeks. Vasomotor symptoms (hot flashes, insomnia) and emotional symptoms (irritability, anxiety, depression) respond rapidly by week 4, while dermatological parameters (skin smoothness, elasticity) and hair health show delayed but pronounced improvements at week 8. All measured endpoints achieved statistical significance versus placebo ($P<0.05$), and no serious adverse events were observed. These findings support EquoPro® S-equol as a safe and effective non-hormonal option for comprehensive perimenopausal symptom management.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

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